AMENDMENTS TO THE SPECIFICATION:

Please delete in its entirety the first paragraph on page 1, and add the following new paragraph in lieu thereof:

This is a continuation of application Serial No. 09/635,845, filed August 11, 2000, now abandoned; which is a continuation of application Serial No. 08/460,673, filed June 2, 1995, now abandoned; which is a continuation of application Serial No. 08/015,987, filed February 10, 1993, now abandoned; which is a continuation-in-part of application Serial No. 07/833,429, filed February 10, 1992, now abandoned; which is a continuation-part of application Serial No. 07/591,109, filed October 1, 1990, now abandoned; which is a continuation-in-part of application Serial No. 07/093,854, filed September 8, 1987, now USP 5,019,387 the entire contents of which are hereby incorporated by reference in this application.

Please amend the paragraph beginning at page 5, line 4, as follows:

The present invention provides a method of modification of peptide immunogens whereby the modification changes a potent immunogen into a potent toleragen. The invention is based on the unexpected observation that the F-domain of HIV-1 gp41 confers to an antigen the ability to be toleragen. Specifically, the hydrophobic N-terminal 12 amino acids of the gp41 envelope protein that mediate fusion of HIV to uninfected cells, the fusogenic (F) domain (M.L. Bosch, et al, Science, 244:694-697, 1989), were added C-terminal to the highly immunogenic T1-SP10 and T1-SP10(A)

peptides (Table 3 (SEQ ID NOs:23 to 25, respectively)) (T.J. Palker, et al, J. Immunol. 142:3612-3619; M.K. Hart, et al, J. Immunol. 145:2677-2685, 1990; M.K. Hart, et al, Proc. Natl. Acad. Sci. USA 88:9448-9452, 1991). When used as an immunogen in chimpanzees, the T1-SP10IIIB and the T1-SP10IIIB(A) peptides were potent immunogens, whereas the F-T1-SP10IIIB(A) peptide (M.K. Hart, et al, Proc. Natl. Acad. Sci. USA 88:9488-9452, 1991) were not as immunogenic at either low (.1mg/kg) or at high (.5 mg/kg) doses. Moreover, challenge of the animals with the highly immunogenic T1-SP10IIIB(A) peptide at month 16 of the immunization schedule proved that the F-T1-SP10IIIB(A) immunized animals were tolerant to the T1-SP10IIIB(A) HIV gp120 env determinants.

Please amend the paragraph beginning at Page 7, line 1, as follows:

Figure 10. Variants of T1-SP10 peptides derived from HIV MN and IIIB Envelope Sequences (SEQ ID NO:16 to SEQ ID NO:23, respectively).

Please amend the paragraph beginning at page 9, line 20 as follows:

An example of this invention for inducing tolerance to antibodies against autoantigens is for the treatment of myasthenia gravis, whereby the F-sequence is synthesized N-terminal to the main immunogenic region of the acetylcholine receptor, **WNPADYGGIK** (SEQ ID NO:1) OR **WNPDDYGGVK** (SEQ ID NO:2) (I. Papdouli, et al, Biochem. J. 269:-245, 1990). The resulting immunogen is

AVGIGALFLGFL**WNPADYGGIK** (SEQ ID NO:3) or

AVGIGALFLGFL**WNPDDYGGVK** (SEQ ID NO:4).

Please amend the paragraph beginning at page 9, line 29, as follows:

Another example of a B cell toleragen is a hybrid protein comprising the HIV fusion domain synthesized either linearly N-terminal to B cell peptide epitopes of the insulin molecule or covalently linked to the whole insulin molecule or covalently linked or constructed using recombinant DNA techniques to a peptide insulin fragment or to the whole insulin molecule. The resulting immunogen is AVGIGALFLGFL (SEQ ID NO:5)-**insulin** or AVGIGALFLGFL (SEQ ID NO:5)-**insulin peptide fragment**. These types of toleragens can be used to prevent the onset of juvenile diabetes mellitus, (J.P. Palmer, et al, Science 222:1337-1339, 1983; B.M. Dean, et al, Diabetologia 23:339-342, 1986) and to treat patients with insulin antibodies in the setting of insulin resulin resistance (J.D. Schnatz, Dolovich, et al, J. Allergy, 46: 127-1137, 1970).

Please amend the paragraph beginning at page 10, line 9, as follows:

Another example of a B cell toleragen is a hybrid protein comprising the HIV fusion domain synthesized either linearly N-terminal to B cell peptide epitopes of the TSH receptor molecule or covalently linked to the whole TSH receptor molecule or covalently linked or constructed using recombinant DNA techniques to a peptide TSH receptor fragment or to the whole TSH receptor molecule. The resulting immunogen is

AVGIGALFLGFL (SEQ ID NO:5)-**TSH receptor** or AVGIGALFLGFL (SEQ ID NO:5)-**TSH receptor peptide fragment**. These types of toleragens can be used to treat autoimmune thyroid disease (Graves' Disease) (T. Mori, et al, Biochem. & Biophy. Res. Comm. 178:165-172, 1991; M. Murakami, et al, Biochem. & Biophy. Res. Comm. 171:512-518, 1990). Table 6 (SEQ ID NOs:36-40, respectively) summarizes B cell epitopes on the thyrotropin (TSH) receptor to which Graves' patient sera bind (T. Mori, et al, Biochem. & Biophy. Res. Comm. 171:165-172, 1991; M. Murakami, et al, Biochem. & Biophys. Res. Comm. 171:512-518, 1990; O. Takai, et al, Biochem. & Biophy. Res. Comm. 179:319-326, 1991; T. Piraphatdis, et al, Biochem. & Biophy. Res. Comm. 172:529-536, 1990). Of interest is the sequence YYVFFEEQEDEIIGF (SEQ ID NO:6) identified by 2 studies that inhibits the TSH activity of the autoantibodies (T. Mori, et al, Biochem. & Biophy. Res. Comm. 178:165-172, 1991; O. Takai, et al, Biochem. & Biophy. Res. Comm. 179:319-326, 1991). Thus constructs for inducing tolerance to anti-TSH antibodies in Graves' disease are

AVGIGALFLGFL**YVFFEEQEDEI** (SEQ ID NO:7) or

AVGIGALFLGFL**HQEEDFRVTCKDIQRIPSLPPSTQT** (SEQ ID NO:8) or

AVGIGALFLGFL**LRQRKSVNALNSPLHQEYEENLGDSIVGY** (SEQ ID NO:9) or

AVGIGALFLGFL**YYVFFEEQEDEIIGF** (SEQ ID NO:10) or

AVGIGALFLGFL**YKELPLLKFL** (SEQ ID NO:11).

Please amend the paragraph beginning at page 11, line 8, as follows:

An example of the use of this invention in the induction of tolerance to autoimmune T cell antigens is a hybrid protein comprised of the HIV fusion domain synthesized either linearly N-terminal to T cell peptide epitopes of the myelin basic protein molecule or covalently linked or constructed using recombinant DNA techniques to a myelin protein molecule. The resulting immunogen is AVGIGALFLGFL (SEQ ID NO:5)-**myelin basic protein** or AVGIGALFLGFL (SEQ ID NO:5)-**myelin basic protein peptide fragment.** In the case of the myelin basic protein peptide fragment, the encephalitogenic T cell epitopes are known, one of which is contained in sequence 69-89 of bovine myelin basic protein (H. Offner, et al, J. Immunol. 141:3828-3832, 1988). In this case, one formulation of the toleragen is AVGIGALFLGFL**GSLPQKSQRSQDENPVVHF** (SEQ ID NO:12). These types of toleragens can be used to treat experimental autoimmune encephalomyelitis, which is thought to be an excellent model of human multiple sclerosis (K.W. Wucherpfenning, et al, Immunol. Today, 12:277-281, 1991). When the specific epitopes are identified that are the T cell targets in multiple sclerosis, then those sequences can be substituted in the peptide above, and used to tolerize T cells to the pathogenic T cell epitope of whatever the protein antigen turns out to be involved in multiple sclerosis.

Please amend the paragraph beginning at page 11, line 36, as follows:

Another example of this invention for induction of tolerance to autoimmune T cell antigens is a hybrid protein comprising the HIV fusion domain synthesized either linearly N-terminal to T cell peptide epitopes of the retinal S protein molecule or covalently linked to the whole retinal S protein molecule or covalently linked or constructed using recombinant DNA techniques to retinal S antigen fragment or to the whole retinal S antigen molecule. The resulting immunogen is AVGIGALFLGFL (SEQ ID NO:5)-**retinal S protein** or AVGIGALFLGFL (SEQ ID NO:5)-**retinal S protein peptide fragment**. In the case of the retinal S protein peptide fragment, the pathogenic T cell epitopes are known, one of which is present in the sequence 1169-1191 of retinal S protein (H. Sanui, et al, Exp. Med., 169:1947-1960, 1989). In this case, one formulation of the toleragen is AVGIGALFLGFL**PTARSVGAADGSSWEGVGVV** (SEQ ID NO:13). These types of toleragens can be used to treat experimental autoimmune retinouveitis, which is thought to be an excellent model of human inflammatory eye diseases such as Bechet's syndrome and idiopathic retinouveitis (H. Sanui, et al, Exp. Med., 169:1947-1960, 1989). When the specific epitopes are discovered that are the T cell targets in human inflammatory eye disease, then those sequences can be substituted in the peptide above, and used to tolerize T cells to the pathogenic T cell epitope of whatever the protein antigen turns out to be in human retinouveitis.

Please amend the paragraph beginning at page 12, line 30, as follows:

For the treatment of pathogenic immune responses induced by an infectious agent, an example of the invention is the treatment of HTLV-I associated myelopathy syndrome seen in tropical spastic paraparesis (rev. in Jacobson et al J. Immunol. 146:1155-1162, 1991). In this disease, there is a strong evidence that the neurologic disease is caused by the induction of cytotoxic T cells (CTL) against HTLV-I infected cells in the central nervous system (S. Jacobson, et al, J. Immunol. 146: 1155-1162, 1991). Jacobson, et al have shown that one primary region of HTLV-I env gp46 that induces CTL in tropical spastic paraparesis (TSP) is aa196-209 of gp46 as defined by peptide SP4a1 (S. Jacobson, et al, J. Immunol. 146:1155-1162, 1991; T.J. Palker, et al, J. Immunol., 142:971-978, 1989; A. Kurata, et al, J. Immunol., 143:2024-2030, 1989). Thus, to treat TSP, the present invention can be embodied by the hybrid peptide AVGIGALFLGFL**LDHILEPSIPWKSKK** (SEQ ID NO:14). When new pathogenic CTL epitopes of HTLV-I are discovered, the therapeutic construct can be F-X where F is the hydrophobic sequence and X is the CTL epitope of the infectious agent.

Please amend the paragraph beginning at page 13, line 17, as follows:

The clinical manifestations of HIV have been postulated to be due to autoimmune responses induced by components of HIV that have sequence homology to human MHC Class I or Class II molecules (G.W. Hoffman, et al, Prac. Natl. Acad. Sci. USA 88:3060-3064, 1991; H. Wigzell, et al, FASEB J. p. 2406-2410, 1991; H. Golding, et al, J. Clin.

Invest. 83:1430-1435; F. Grassi, et al, J. Ex. Med., 174:53-62, 1991; J.A.T. Young, Nature, 333:215, 1988; H. Golding, et al, J. Exp. Med., 167:914-923, 1988). For the treatment of HIV infection, the present invention can comprise a series of hybrid peptides, each peptide containing an N-terminal hydrophobic peptide such as the HIV gp41 fusion domain (Table 5 (SEQ ID NOs:26-35, respectively)) and a C-terminal peptide from each of the regions of HIV env proteins bearing sequence homology MHC class I or class II molecules (G.W. Hoffman, et al, Prac. Natl. Acad. Sci. USA 88:3060-3064, 1991; H. Wigzell, et al, FASEB J. p. 2406-2410, 1991; H. Golding, et al, J. Clin. Invest. 83:1430-1435; F. Grassi, et al, J. Ex. Med., 174:53-62, 1991; J.A.T. Young, Nature, 333:215, 1988; H. Golding, et al, J. Exp. Med., 167:914-923, 1988) (Table 7 (SEQ ID NOs:41-48, respectively)). Alternatively, it may be advantageous to treat HIV infected individuals with F-X peptides where F is a hydrophobic peptide such as the fusogenic domain of HIV and X is a peptide fragment of HIV that is immunogenic to T or B cells. In this situation, a mixture of peptides would be used to inhibit destructive anti-HIV immune responses that were damaging host HIV-infected antigen-presenting cells. Examples of this type of peptide are shown in Table 3 and Figure 10, and were the peptides used that tolerized chimpanzees in Figures 1 and 2 to both T1-SAP10(A) determinants and to whole gp120 protein (Table 4).

Please amend the paragraph beginning at page 23, line 33, as follows:

Using a previously described strategy of breaking B cell tolerance by immunization with an immunogen that is different from, but structurally related to, the tolerogen (Weigle, Natural and Acquired Immunologic Unresponsiveness (1967) Chapter 4, pp. 57-151), animals 1045 and 1070 were next immunized with the HIVMN Th-B peptide. The TH-B peptide from HIVMN contained the same Th (T1) gp 120 sequence as the HIVIIIB Th-B peptide, but contained different B cell gp 120 V3 B cell epitope sequences than those in the HIVIIIB Th-B peptide (Table 8 (SEQ ID NOs:23, 22, 24 and 17, respectively)). After 2 immunizations with Th-B of HIVMN, beginning at month 17, both chimpanzee nos. 1045 and 1070 had prompt rises in titer of antibodies to HIVIIIB (Table 9) and to HIVMN Th-B peptide (not shown) to antibody levels that were higher than had previously been obtained during the prior 18 months of study. At month 20, endpoint ELISA titers to the HIVMN Th-B peptide were 1:102,400 for animal 1045 and 1:204,800 for animal 1070.

Please amend the paragraph beginning at page 29, line 1, as follows:

To determine why antibodies against HIVIIIB Th-B peptides did not neutralize HIVIIIB in vitro during the first 17 months of immunization, sera from the early peak anti-HIVIIIB peptide antibody responses (month 6) were assayed for reactivity to the individual epitopes of the Th-B peptides. It was found that at the time of initial titers of anti-Th-B peptide responses, most of the antibody reactivity in sera from animals 884 and

1028 was indeed directed to the primary amino acid sequence of the neutralizing V3 loop region defined by the peptide (TRKSIRIQRGPGR) (SEQ ID NO:15) (Table 12 (SEQ ID NOs:49-53, respectively,). These data indicate that antibodies made by chimpanzee nos. 884 and 1028 at 7 months after immunization with the HIVIIIB Th-B HIV env peptides did not recognize the appropriate secondary V3 loop structure(s) necessary for neutralizing HIVIIIB, although the animals did make antibody responses to the correct primary amino acid sequences of the neutralizing V3 B cell determinant of HIVIIIB gp120.